FIGURE 1

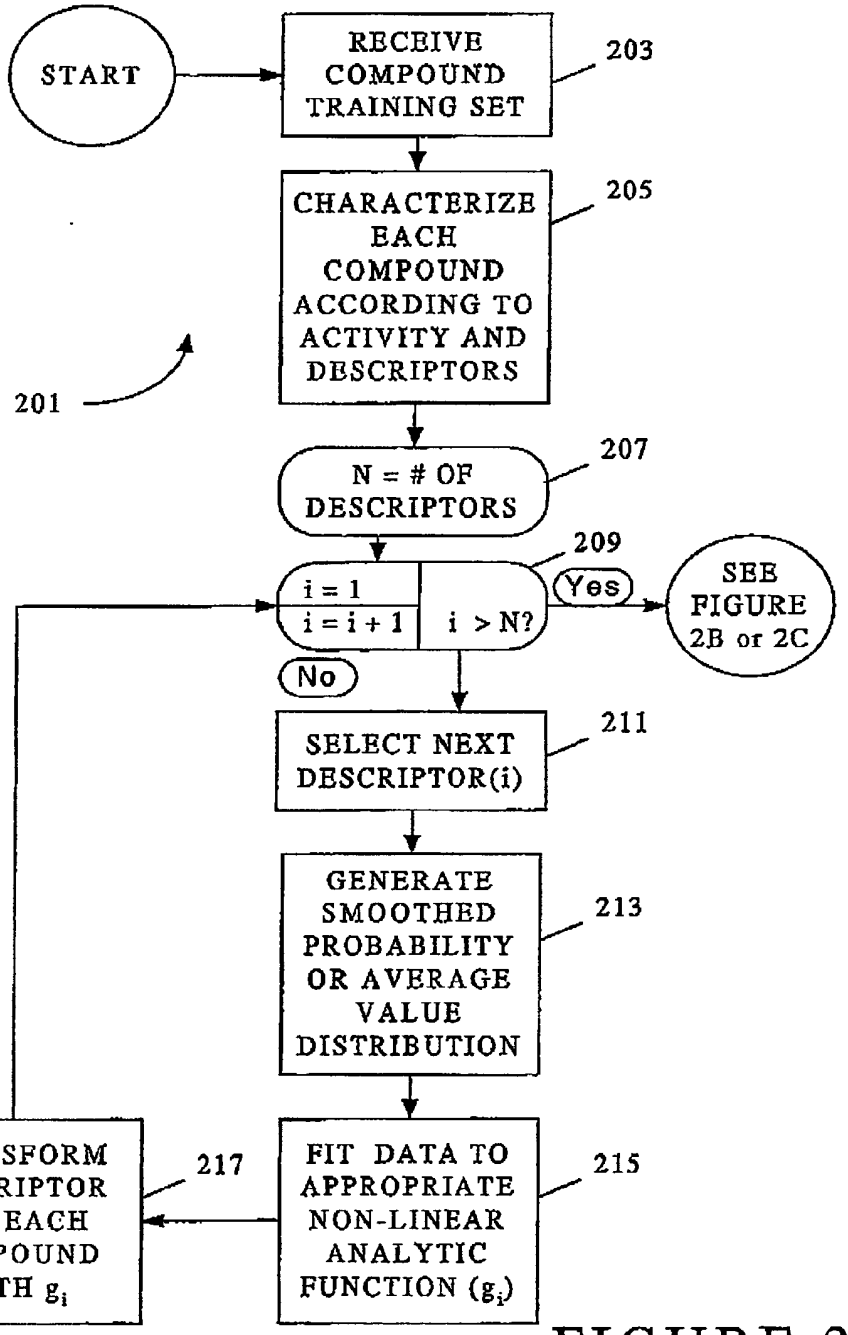


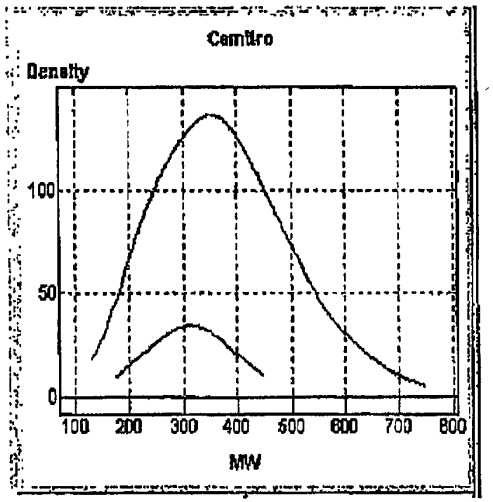
FIGURE 2A

FIGURE 2B

FIGURE 2C

FIGURE 3

Optimum Molecular Weight



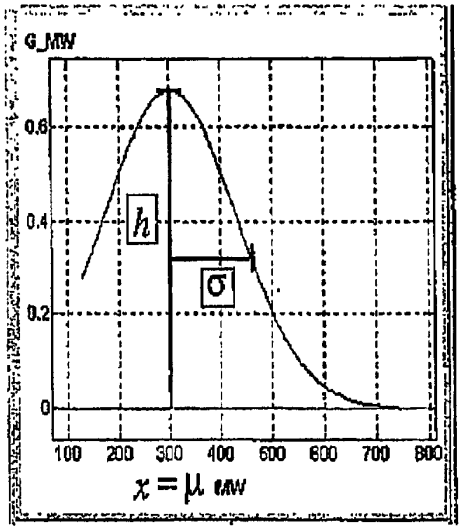


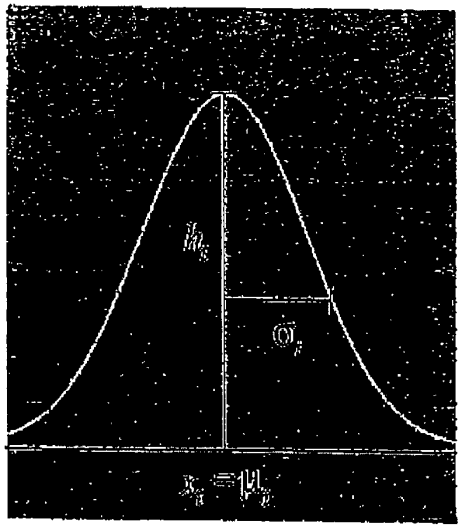
FIGURE 4A

$$g(x) = he^{-(x-\mu)^2/4\sigma^2}$$

N-Dimensional Gaussian Modeling

Additive

$$g(x_{i..N}) = \frac{1}{N}\sum_{i=1}^{N} h_i e^{-(x_i-\mu_i)^2/4\sigma_i^2}$$



Multiplicative

$$g(x_{i..N}) = h e^{-\frac{1}{N}\sum_{i=1}^{N}(x_i-\mu_i)^2/4\sigma_i^2}$$

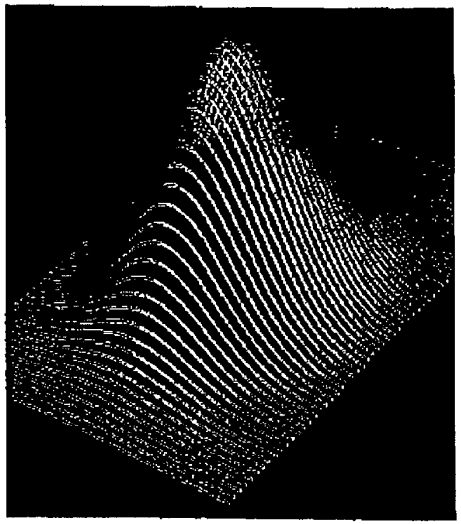


FIGURE 4B

Optimization Function

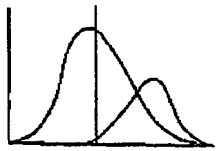
$$g(\mathbf{x}, \mu, \sigma, h, t) = t + he^{-\sum_{k=1}^{N_x}(x_k-\mu_k)^2 / 4\sigma_k^2}$$

$$f = s_{inh}\left[\frac{1}{N_{inh}}\sum_{i=1}^{N_{inh}}\left(g(\mathbf{X}_i, \mu, \sigma, h, t) - y_i\right)^2\right]$$

Mean of the Squared Errors of Inhibitor Affinity

$$+ s_{drug}\left[\frac{1}{N_{drug}}\sum_{j=1}^{N_{drug}} g(\mathbf{X}_j, \mu, \sigma, h, t) - \bar{y}_{drug}\right]^2$$

Squared Error of the Means of Drug Affinity



$$+ s_{fit}\left[\sigma_y^2 \sum_{k=1}^{N_x}\left(\frac{\mu_k - \mu_{0,k}}{range(\mathbf{X}_k^T)}\right)^2 + (t - t_0)^2\right]$$

Constraints to prevent Overfitting

FIGURE 4C

Initial Values for Optimization

$$t_0 = min(\mathbf{y})$$

$$h_0 = max(\mathbf{y}) - t_0$$

$$\mu_{0,k} = \frac{\sum_{i=1}^{N_{inh}} (y_i - t_0)^2 x_{k,i}}{\sum_{i=1}^{N_{inh}} (y_i - t_0)^2}$$

$$\sigma_{0,k} = \sqrt{\frac{\sum_{i=1}^{N_{inh}} (y_i - t_0)^2 (x_{k,i} - \mu_k)^2}{\sum_{i=1}^{N_{inh}} (y_i - t_0)^2}}$$

$$\sigma_y = \sqrt{\frac{\sum_{i=1}^{N_{inh}} (y_i - \bar{y}_{inh})^2}{N_{inh} - 1}}$$

FIGURE 4D

Gaussian Optimization Function

$$f(\mathbf{x}) = t + he^{-\sum_{k=1}^{N_x}(x_k - c_k)^2 / 4w_k^2}$$

$$f_o = s_y \left(\frac{\sum_{i=1}^{N_y} u_i (f(\mathbf{x}_i) - y_i)^2}{\sigma_y^2 \sum_{i=1}^{N_y} u_i} \right)$$ Weighted Mean Squared Error

$$+ \; s_c \sum_{k=1}^{N_x} \frac{(c_k - c_{0,k})^2}{\sigma_{x_k}^2}$$ Center Constraint

$$+ \; s_w \sum_{k=1}^{N_x} \frac{\sigma_{x_k}}{w_k}$$ Width (Focus) Constraint

$$+ \; s_t \frac{(t - t_0)^2}{\sigma_y^2}$$ Tare Constraint

FIGURE 4E

Gaussian Optimization
Starting Values

$$\sigma_y^2 = \frac{\sum_{i=1}^{N_{hits}} u_i (y_i - \bar{y})^2}{\sum_{i=1}^{N_{hits}} u_i}$$

$$\sigma_{x_k}^2 = \frac{\sum_{i=1}^{N_{hits}} u_i (x_{k,i} - \bar{x}_k)^2}{\sum_{i=1}^{N_{hits}} u_i}$$

$$t_0 = min(\mathrm{y})$$

$$h_0 = max(\mathrm{y}) - t_0$$

$$v_i = \frac{(y_i - t_0)^2}{\sigma_y^2}$$

$$c_{0,k} = \frac{\sum_{i=1}^{N_{hits}} u_i v_i x_{k,i}}{\sum_{i=1}^{N_{hits}} u_i v_i}$$

$$w_{0,k}^2 = \frac{\sum_{i=1}^{N_{hits}} u_i v_i (x_{k,i} - c_{0,k})^2}{\sum_{i=1}^{N_{hits}} u_i v_i}$$

FIGURE 4F

Performance Metrics

$$n_k = \frac{\sigma_{x_k}}{w_k}$$

Descriptor Focus

$$s = \sqrt{\frac{\sum_{i=1}^{N_y} u_i \left(f(\mathbf{x}_i) - y_i\right)^2}{\sum_{i=1}^{N_y} u_i}}$$

Standard Error

$$r^2 = \frac{\left(\sum_{i=1}^{N_y} u_i \left(f(\mathbf{x}_i) - \bar{f}(\mathbf{x})\right)\left(y_i - \bar{y}\right)\right)^2}{\sum_{i=1}^{N_y} u_i \left(f(\mathbf{x}_i) - \bar{f}(\mathbf{x})\right)^2 \sum_{i=1}^{N_y} u_i \left(y_i - \bar{y}\right)^2}$$

Correlation Coefficient

$$q^2 = 1 - s^2 / \sigma_y^2$$

Residual Error

FIGURE 4G

FIGURE 4H

Sigmoid Optimization Function

$$f(\mathbf{x}) = t + \frac{h}{1 + \sum_{k=1}^{N_x} e^{-n_k(x_k - c_k)}}$$

$$f_o = s_y \left(\frac{\sum_{i=1}^{N_y} u_i \left(f(\mathbf{x}_i) - y_i \right)^2}{\sigma_y^2 \sum_{i=1}^{N_y} u_i} \right)$$ Weighted Mean Squared Error

$$+ \; s_c \sum_{k=1}^{N_x} \frac{\left(c_k - c_{0,k} \right)^2}{\sigma_{x_k}^2}$$ Center Constraint

$$+ \; s_n \sum_{k=1}^{N_x} |n_k| \sigma_{x_k}$$ Focus Constraint

$$+ \; s_t \frac{\left(t - t_0 \right)^2}{\sigma_y^2}$$ Tare Constraint

FIGURE 4I

Sigmoid Optimization Starting Values

$$t_0 = min(\mathrm{y})$$

$$h_0 = max(\mathrm{y}) - t_0$$

$$v_i = \frac{(y_i - t_0)^2}{\sigma_y^2}$$

$$v_i' = \frac{(h_0 + t_0 - y_i)^2}{\sigma_y^2}$$

$$c_{h,k} = \frac{\sum_{i=1}^{N_{fuzb}} u_i v_i x_{k,i}}{\sum_{i=1}^{N_{fuzb}} u_i v_i}$$

$$c_{l,k} = \frac{\sum_{i=1}^{N_{fuzb}} u_i v_i' x_{k,i}}{\sum_{i=1}^{N_{fuzb}} u_i v_i'}$$

$$c_{0,k} = \frac{c_{h,k} + c_{l,k}}{2}$$

$$w_{h,k} = \sqrt{\frac{\sum_{i=1}^{N_{fuzb}} u_i v_i (x_{k,i} - c_{h,k})^2}{\sum_{i=1}^{N_{fuzb}} u_i v_i}}$$

$$w_{l,k} = \sqrt{\frac{\sum_{i=1}^{N_{fuzb}} u_i v_i' (x_{k,i} - c_{l,k})^2}{\sum_{i=1}^{N_{fuzb}} u_i v_i'}}$$

$$n_{0,k} = \frac{c_{h,k} - c_{l,k}}{w_{h,k} w_{l,k}}$$

FIGURE 4J

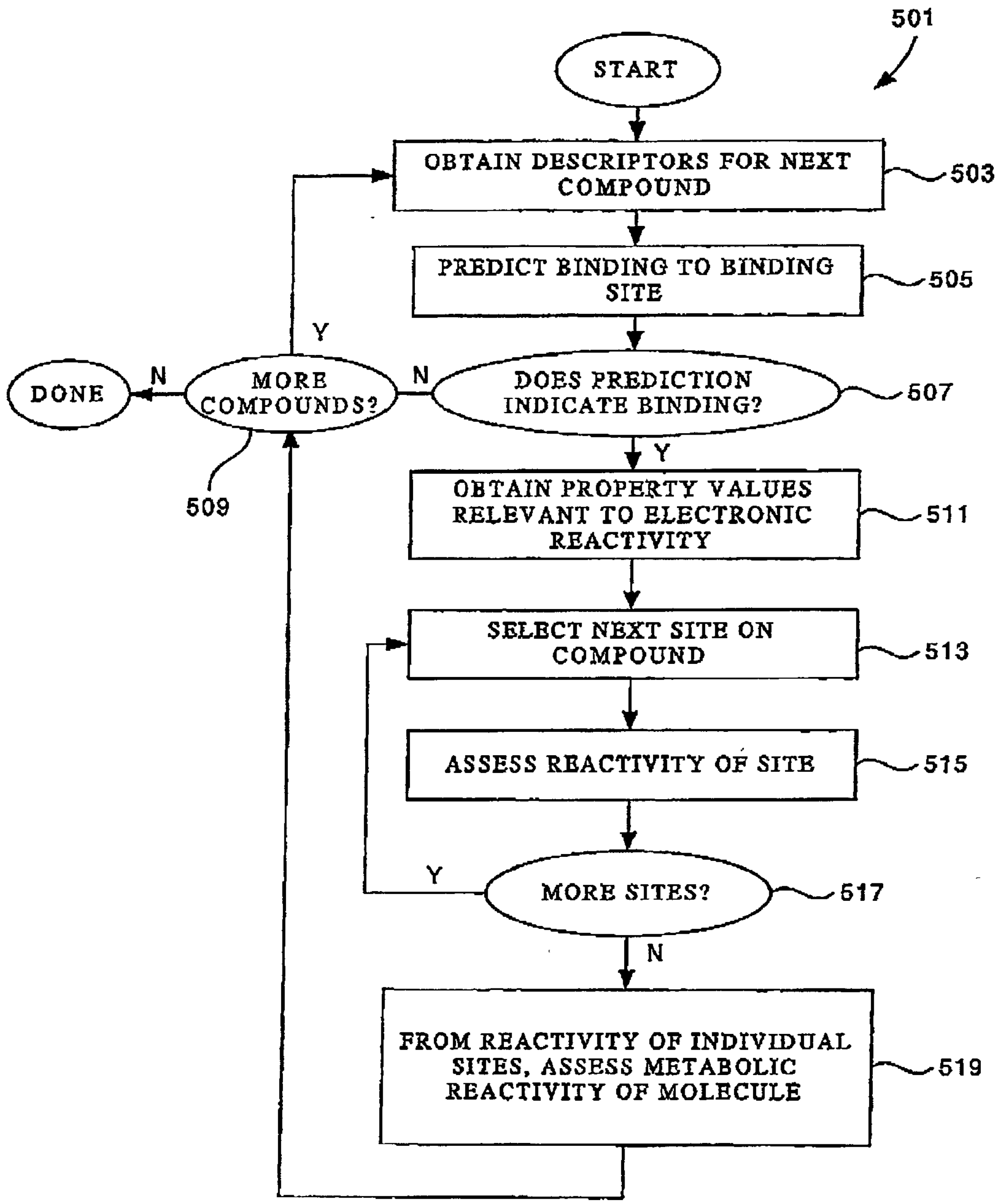


FIGURE 5

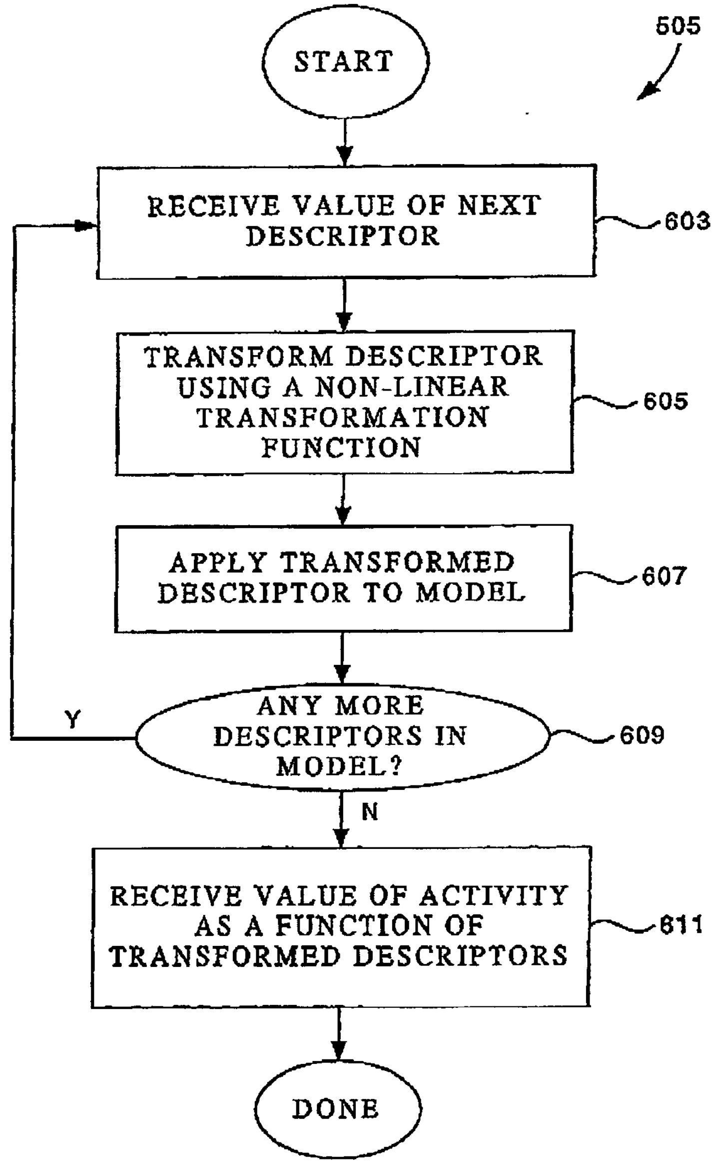


FIGURE 6

Optimum logP

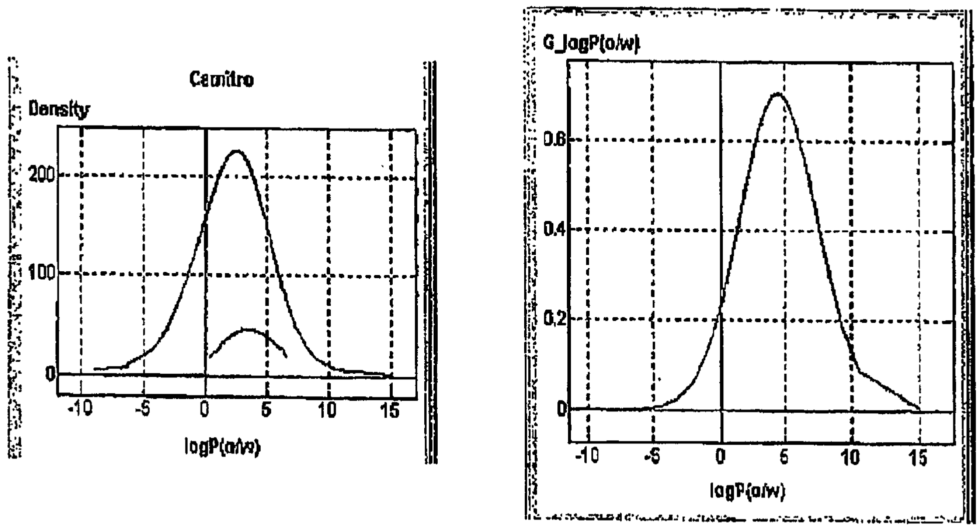
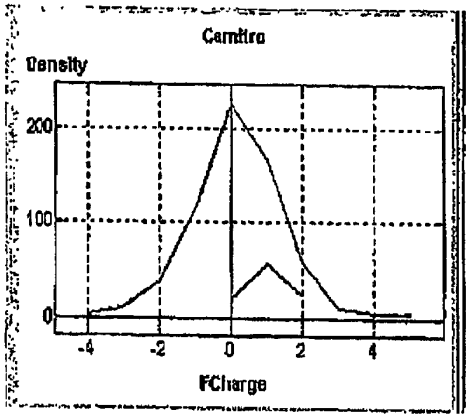


FIGURE 7A

Optimum Formal Charge



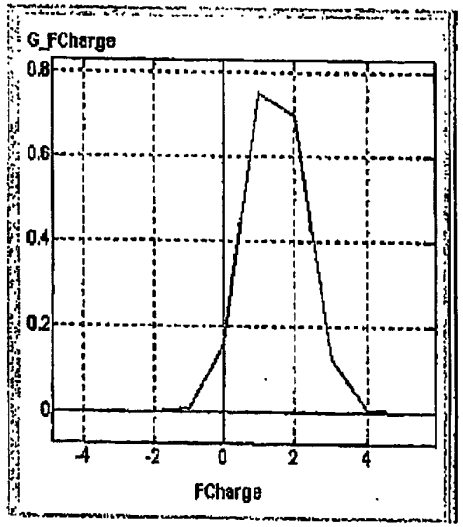
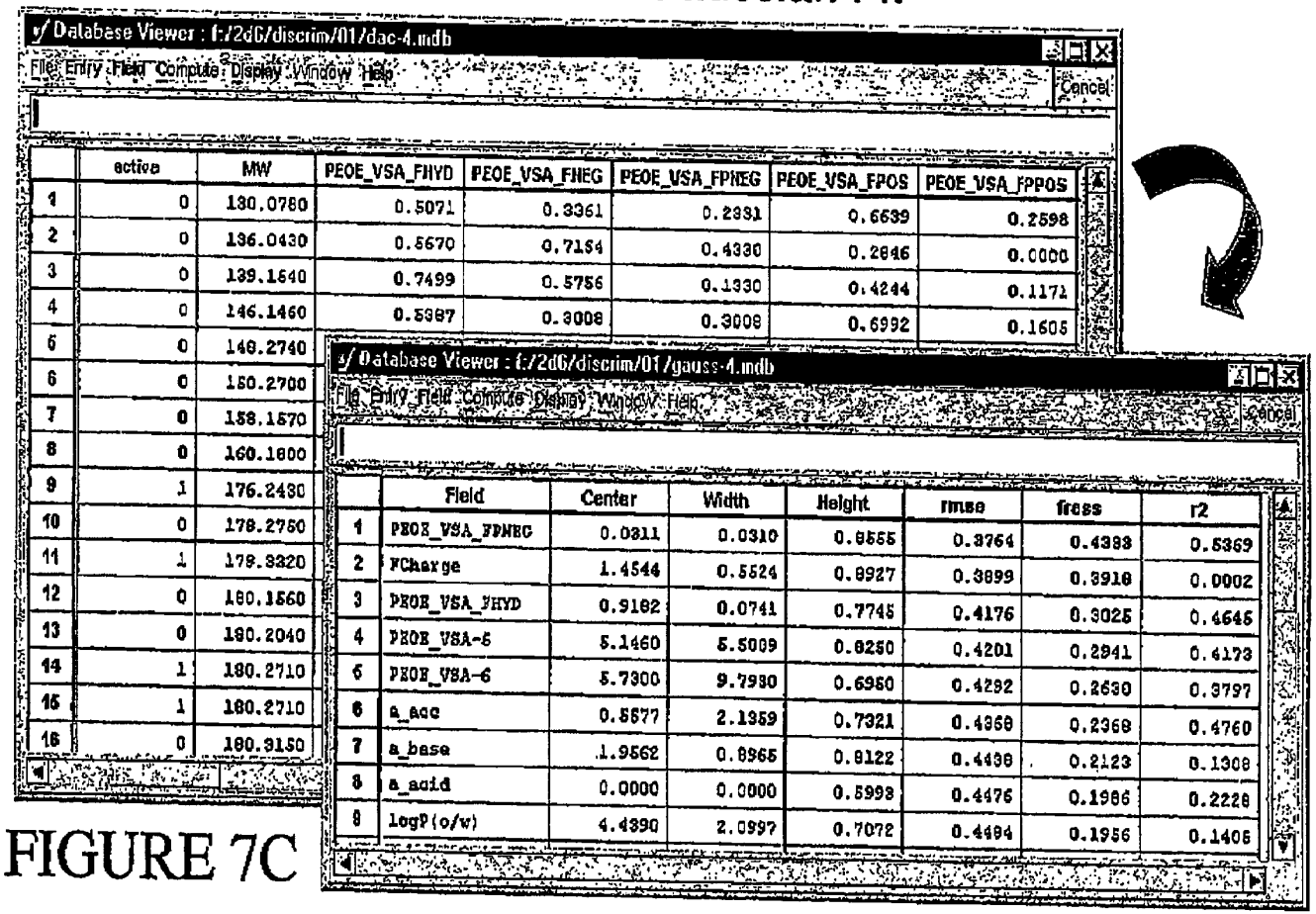


FIGURE 7B

Automated Gaussian Fit



	active	MW	PEOE_VSA_FHYD	PEOE_VSA_FNEG	PEOE_VSA_FPNEG	PEOE_VSA_FPOS	PEOE_VSA_FPPOS
1	0	130.0780	0.5071	0.3361	0.2331	0.6639	0.2598
2	0	136.0430	0.5670	0.7154	0.4330	0.2846	0.0000
3	0	139.1540	0.7499	0.5756	0.1330	0.4244	0.1171
4	0	146.1460	0.5387	0.3008	0.3008	0.6992	0.1605
5	0	148.2740					
6	0	150.2700					
7	0	158.1570					
8	0	160.1800					
9	1	176.2430					
10	0	178.2750					
11	1	178.3320					
12	0	180.1550					
13	0	180.2040					
14	1	180.2710					
15	1	180.2710					
16	0	180.3150					

	Field	Center	Width	Height	rmse	fress	r2
1	PEOE_VSA_FPNEG	0.0311	0.0310	0.8555	0.3764	0.4383	0.5369
2	FCharge	1.4544	0.5524	0.8927	0.3899	0.3918	0.0002
3	PEOE_VSA_FHYD	0.9182	0.0741	0.7745	0.4176	0.3025	0.4645
4	PEOE_VSA-5	5.1460	5.5009	0.8250	0.4201	0.2841	0.4173
5	PEOE_VSA-6	5.7300	9.7930	0.6950	0.4292	0.2630	0.3797
6	a_acc	0.5577	2.1359	0.7321	0.4358	0.2368	0.4760
7	a_base	1.9562	0.8365	0.8122	0.4438	0.2123	0.1308
8	a_acid	0.0000	0.0000	0.5998	0.4476	0.1986	0.2228
9	logP(o/w)	4.4390	2.0997	0.7072	0.4494	0.1956	0.1405

FIGURE 7C

2D6 K_i Model

Non-linear Size Relation

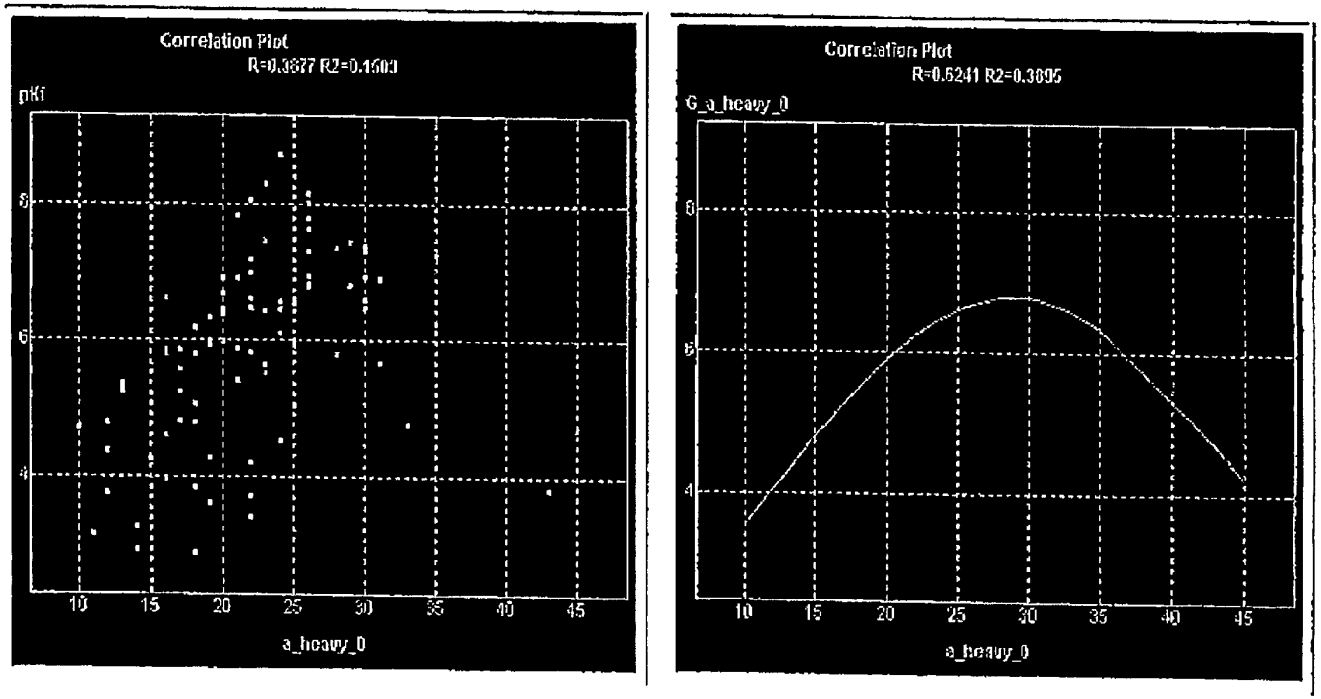


FIGURE 7D

FIGURE 8A

FIGURE 8B

FIGURE 9